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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,186	06/19/2002	James C Liao	06497-013002	2905
7590		12/29/2005		
Fish & Richardson				
225 Franklin Street				
Boston, MA 02110-2804				
EXAMINER				
PROUTY, REBECCA E				
ART UNIT		PAPER NUMBER		
1652				

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

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<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/048,186	LIAO, JAMES C	
	<b>Examiner</b>	<b>Art Unit</b>	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 October 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) Claims 5, 12-13, 21-24, 38, 40, 45, 47-50, 52-75 is/are pending in the application.
- 4a) Of the above claim(s) 22, 38, 49, 52-54, 58-60 and 63-74 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 13, 21, 23, 24, 45, 55-57 and 75 is/are allowed.
- 6) ☒ Claim(s) 5, 12, 40, 47, 48, 61 and 62 is/are rejected.
- 7) ☒ Claim(s) 50 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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Claims 1-4, 6-11, 14-20, 25-37, 39, 41-44, 46 and 51 have been canceled. Claims 5, 12-13, 21-24, 38, 40, 45, 47-50, 52-74 and newly presented claim 75 are still at issue and are present for examination.

Applicants' arguments filed on 10/5/05, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 22, 23, 38, 47-50, 52-54, 56 and 57-74 remain withdrawn from further consideration pursuant to CFR 1.142(b) as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Claims 5, 12, 13, 21, 24, 40, 45, 55 and 75 are examined herein.

Claim 40 is objected to because of the following informalities: "phytoene saturase" on line 7 should be "phytoene desaturase". Appropriate correction is required.

Claims 5 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *E. coli* having an inactivating *glnL* mutation which are transformed with a nucleic acid encoding one or more of the enzymes isopentenyl diphosphate isomerase, geranylgeranyl diphosphate synthase, 1-deoxyxylulose 5-phosphate synthase and

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phosphoenol pyruvate synthase operably linked to the *glnAp2* promoter, kits comprising an *E. coli* having a *glnL* mutation and a nucleic acid encoding the *glnAp2* promoter or nucleic acid constructs therefore, does not reasonably provide enablement for *E. coli* having an inactivating *glnL* mutation which are transformed with a nucleic acid encoding any any isoprenoid precursor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is as was explained in the previous Office Action. Claim 12 is now included in the rejection in view of the amendments to the claims such that the nucleic acid within the claimed host cell is no longer limited to one which encodes an enzyme catalyzing the synthesis of an **isoprenoid** precursor of lycopene,  $\beta$ -carotene or astaxanthin but now includes nucleic acids which encodes any enzyme catalyzing the synthesis of any precursor of lycopene,  $\beta$ -carotene or astaxanthin. As lycopene,  $\beta$ -carotene and astaxanthin are all isoprenoids which are synthesized from isopentenyl diphosphate which is synthesized in *E. coli* from the glycolytic pathway intermediates pyruvate and glyceraldehyde-3-phosphate or acetyl-CoA, virtually any glycolytic pathway or Krebs cycle

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intermediate as well as a large number of additional compounds could be considered to be within the scope of a precursor of lycopene,  $\beta$ -carotene or astaxanthin. As such the number of genes encompassed in the instant claims is enormous and the experimentation to make any use the entire scope would be undue for the reasons previously of record.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 5, 12, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liao (WO96/08567) in view of Bock et al. (US Patent 5,830,692), McCleary et al. (Reference AL of applicant's PTO-1449), McCleary et al. (Reference AM of applicant's PTO-1449) and Haldiman et al. (Reference AK of applicant's PTO-1449) or Feng et al. (Reference AJ of applicant's PTO-1449).

Liao teach constructs for the recombinant expression of phosphoenol pyruvate synthase (pps) in cells producing aromatic metabolites and that the increased expression of pps is useful for increasing the amount of carbon flow into the aromatic

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pathway by producing increased amounts of DAHP. The constructs of Liao comprise the pps gene under the control of an inducible promoter. (see pages 18-19). Liao further shows that cells lacking induction of the pps gene produce significant amounts of the fermentation byproduct acetate indicating significant flux away from PEP and the aromatic pathway (see pages 22-23) but that induction of the pps gene produces undetectable levels of acetate in the cells and near theoretical yields of DAHP.

Bock teach that inducible promoters such as lac, tac, and trp promoters possess several disadvantages in relation to their use for industrial production. These are that the repressors and inducers necessary for use of these promoters are expensive and difficult to handle, particularly when they are metabolizable substances (such as lactose and tryptophan), and cannot be induced completely when the repressor is present in molar excess. (see columns 1-2).

McCleary (AK) and McCleary (AP) teach that acetyl phosphate may act a global regulatory signal in *E. coli* responsible for the activation of a wide range of response regulators of two-component systems, including the *glnAp2* promoter, in the absence of their cognate histidine kinase (i.e., the *ntrB* gene product in the case of *glnAp2*). They further teach that acetyl-

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phosphate levels in bacteria correlate with the amount of acetate produced.

Haldiman et al. and Feng et al. each teach *E. coli* two-component system promoters (the *VanH* promoter in Haldiman et al. and the *glnAp2* promoter in Feng et al.) which are activated by a response regulator protein (*VanR* in Haldiman et al. and *NtrC* in Feng et al.) and acetyl phosphate in the absence of the corresponding histidine kinases (*VanS* in Haldiman et al. and *NtrB* in Feng et al.) and in the presence or absence of nitrogen.

As inducers (IPTG) for promoters such as *tac* used by Liao are expensive and have disadvantages as taught by Bock, it would have been obvious to one of ordinary skill in the art to link the production of pps to the presence of a metabolite in the cell which signals that significant amounts of carbon are being diverted away from the aromatic biosynthetic pathway. Liao teach that acetate production occurs under these conditions. Therefore, it would have been obvious to one of ordinary skill in the art to replace the *tac* promoters in the constructs of Liao with a promoter which is induced by high acetate levels. As McCleary et al. (AK and AP) teach that acetyl-phosphate levels correlate with the amount of acetate produced, it would have been obvious to one of ordinary skill in the art to link the pps gene to the acetyl-phosphate regulated promoters taught

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by Haldiman et al. or Feng et al. and express these constructs in *E. coli* cells which lack the cognate histidine kinases such that the response regulators which activate transcription from these promoters are activated by acetyl phosphate. Furthermore, it would have been obvious to one of ordinary skill in the art to put the cells and vectors necessary for production or high levels of aromatic metabolites together in a kit for easy handling.

Claims 13, 21, 24, 45, 55, and 75 are allowed.

Claims 13, 21, 24, 45, 55, and 75 are directed to an allowable products. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims 23, 47, 48, 50, 56, 57, 61, and 62 directed to the processes of using the patentable products, previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Process claims 23, 47, 48, 50, 56, 57, 61, and 62 are hereby rejoined and fully examined for patentability under 37 CFR 1.104. In accordance with the Official Gazette notice, *supra*, process claims 22, 38, 49, 52-54, 58-60 and 63-74, which do not depend from or otherwise include all the limitations of the allowable products, have NOT been rejoined.



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Claim 50 is objected to because of the following informalities: the word "which" needs to be inserted following "claim 23 in". Appropriate correction is required.

Claims 47, 48, 61 and 62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 (from which claims 48, 61 and 62 depend) lacks antecedent basis for "in which the culturing" as the method of Claim 23 (from which claim 47 depends) does not recite a step of culturing the host cell.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Rebecca Prouty  
Primary Examiner  
Art Unit 1652